REMARKS

Claims 48-178 are presently pending in the application. Claims 124-178 are withdrawn, as discussed in greater detail below. Claims 48-85, 87-110, and 112-123 stand rejected under 35 U.S.C. § 103(a) over WO90/15070 ("Pirrung") in view of WO 89/10977 ("Southern") and US 4,877,745 ("Hayes") and US 4,937,593 ("Prats"). Claims 76, 86, and 111 stand rejected under 35 U.S.C. § 103(a) over Pirrung in view of US 3,615,240 ("Sanz") and US 5,306,510 ("Meltzer"). Applicants respectfully traverse all rejections.

I. Restriction Requirement

The Examiner is requiring Applicants to restriction prosecution between the invention of Group I (claims 48-123), which is directed to an automated method of forming an array of polymers on a support and the invention of Group II (claims 124-178), which is directed to an automated apparatus for forming an array of polymers on a support having one or more localized areas. Applicants respectfully traverse the restriction requirement. However to advance prosecution of this case, Applicants elect Group I (claims 48-123) for prosecution on the merits.

II. The Objection to the Disclosure Is Overcome

The disclosure is objected to for incorrectly indicating the priority status of the present application in the paragraph beginning at page 1 immediately following the title. Specifically, Applicants inadvertently and incorrectly indicated that 07/796,243, filed November 22, 1991 is a continuation-in-part of 07/874,849, filed April 24, 1992. Applicants have correctly indicated the priority status of the present application in the above amendment to the specification. The above amendment to the specification further reflects the updated status of USSN 08/426,202 by

indicating that it issued as US Patent No. 6,136,269. Accordingly, the objection to the disclosure is overcome.

III. Claims 48-85, 87-110, and 112-123 Are Patentable over Pirrung in View of Southern, Hayes, and Prats

Claims 48-85, 87-110, and 112-123 stand rejected under 35 U.S.C. § 103(a) over Pirrung in view of Southern, Hayes, and Prats. Applicants respectfully traverse this rejection in view of the following remarks.

The Examiner states at page 4 of the present Office Action that Pirrung fails to teach depositing by a dispenser as presently claimed. Since the Examiner states that Pirrung does not teach such depositing by a dispenser, it thus follows that Pirrung also does not teach positioning the dispenser as addressed in several of the dependent claims.

Southern does not cure the deficiencies of Pirrung. The Examiner has apparently cited Southern for its supposed teaching of the use of an ink jet printer to deposit monomers. However, Southern readily admits at page 11, lines 14-18 that "automatic equipment for applying the precursors has yet to be developed, but there are obvious possibilites [sic: possibilities]; it should not be difficult to adapt a pen plotter or other computer-controlled printing device to the purpose." This statement of Southern represents no more than an invitation to experiment which is not the proper standard for determining obviousness of the claimed invention. In stark contrast to this statement, Southern teaches a method of depositing a monomer by flushing a solution of the monomer by syringe injection over the entire surface of an enclosed substrate and not by an ink jet printer on the surface of the substrate.

The substrate on which Southern "built" oligonucleotides is described at page 15 line 35 to page 16 line 13 as a sandwich of a derivatized microscope slide, a silicone rubber boundary

defining the patch to be synthesized and a piece of teflon to create a cavity. To the cavity was fitted with a short piece of plastic tubing that allowed Southern to inject and withdraw the coupling solution by syringe and to flush the cavity with argon. It is apparent that the method used by Southern to deposit monomer was to flush coupling solution over the entire derivatized surface and not by dispensing droplets, such as by way of an ink jet printer. This approach is confirmed in Example 3 which describes the use of silicone rubber tubing to form a cavity into which coupling solution was introduced through a syringe and to the laying down of bases in longitudinal stripes using a mask. Accordingly, no motivation is provided by Southern to use an ink jet printer to deposit monomers in an apparatus for forming an array of substances on a support, because Southern provides no reasonable expectation of success in so doing.

Importantly, later publications by Southern demonstrate the problems Southern encountered in creating arrays of any sufficient density or sufficiently small cell size on the order presently claimed by applicants using his technology. (See for example claim 67 reciting a localized area of 100 μm^2 with claims 99 and 100 reciting densities of localized areas of 1000 and 10,000 per cm^2, respectively.) At page 1014, paragraph 5 of Southern et al. "Analyzing and Comparing Nucleic Acid Sequences by Hybridization to Array of Oligonucleotides: Evaluation Using Experimental Models", *Genomics* 13, 1008-1017 (1992), Southern discloses that "[a]n array of all octanucleotides would occupy an area 256 x 256 mm with a cell size of 1 mm^2, which is probably close to the limit of the method described here . . . ." For creating smaller arrays, Southern relies on the teachings of Fodor et al., "Light-directed, Spatially Addressable Parallel Chemical Synthesis," *Science*, 251:767-773 (1991):

> Printing methods with a resolution of 10 μm could be used to form masks resistant to the oligonucleotide precursors or the deprotecting agents. Photolithographic techniques can be used to remove photolabile blocking groups at each cycle of synthesis. (Fodor, et al., 1991). This method can produce cells

> down to a size of 25 μm. Such small cell sizes would produce a device 40-100 mm square for an array of all dodecamers, with the potential to analyze runs of around 4000 bases.

Id.

In a still later publication, Southern still is unable to use his methods to obtain an array of any sufficient density. "Our methods limit us to a cell size of less than 2 mm, whereas the photodeprotection method can give cells 50 μm square." Southern & Maskos, "Parallel Synthesis and Analysis of Large Number of Related Chemical Compounds: Applications to Oligonucleotides", *Journal of Biotechnology* 35 (1994) at page 221, paragraph 3. At page 225 of that same reference, Southern states that:

> the limit for our physical separation of channels is likely to be in the 1 mm range and is therefore sufficient for 8-mer arrays with an array size of approximately 25 cm x 25 cm. To decrease cell size further, a number of alternatives can be pursued.
>
> Photolithography (Fodor, et al., 1991) is one possibility to synthesize oligonucleotides in patches of down to 50 μm x 50 μm. The key parameter to be improved are stepwise yield, currently 80-95%, and the possibility to completely mask off areas of the plate that are not supposed to take part in any given deprotection step, which would otherwise result in failure sequences. This point is difficult to address given the relatively long deprotection times (of the order of 30 min) required.

Further, Hayes and Prats also fail to cure the deficiencies of Pirrung. Hayes does not teach or suggest an automated method for forming an array of polymer substances on a support as recited by the claims. At the outset, Hayes does not describe repeatedly dispensing monomers for the purpose of building polymers. Hayes merely teaches "reagent fluids" as described throughout its disclosure. Furthermore, Hayes acknowledges problems with printing in the demand mode (i.e., printing other than in a continuous line) when using low viscous fluids. "Developing stable and reproducible demand mode jetting is difficult with very low viscosities. Although droplet emission can be established at some fundamental frequencies, the droplets

dispensed may have small satellite droplets which reduce the accuracy for metering and dispensing applications." See Col. 18 lines 32-36. Applicants respectfully submit that the above disclosure amounts to a teaching against the use of the printing device of Hayes for array production. Hayes then teaches that even with the problems of accuracy due to satellite drops, "sufficient reagent is adequately delivered for most print applications without a substantial decrease in print quality." Col. 18 lines 37-40. Hayes does not identify what type of printing application is contemplated, however, it is assumed that the printing application is one where minute quantities of fluid intended to be deposited in a specific dense pattern, as in array production, is not being referenced.

In contrast to array production on a support as claimed, the printing embodiments of Hayes are very clearly directed to dispensing reagents onto filter paper test strips (Col. 2 lines 4-7), although Hayes generically refers to a "print medium" at col. 3 line 37. The filter paper embodiment is further discussed as being advantageous insofar as the reagent fluid is rapidly absorbed "thereby allowing rapid and precise placement of a variety of reagents on the target **1** with reduced drying time and reduced potential of fluidic mixing." Col. 14 lines 3-7. Absorption into the filter paper, therefore, is the means by which reagent is retained in the filter paper. Hayes further describes printing a high density matrix on the filter paper medium, presumably because of the ability of the filter paper to absorb the fluid reagent. "In addition, the ability to place small droplets **2** in a precise manner enables the target **1** to be printed in a high density matrix with a variety of reagents as isolated matrix elements." Col. 14 lines 7-10. However, filter paper test strips are not arrays within the scope of the present invention.

In addition to Hayes failing to teach or suggest array manufacture on a support for the reasons set forth above by applicants, the Examiner states that Hayes fails to teach positioning

the print head as is addressed in several dependent claims. Prats fails to cure these deficiencies. The Examiner has cited Prats for its supposed teaching of positioning the print head in X, Y, and Z directions to enhance printing. Applicants, however, respectfully disagree with the Examiner's assertion.

Prats does not teach or suggest an automated method for forming an array of polymers as claimed and therefore does not cure the deficiencies of Hayes. Prats is relied upon solely for its optical positioning system. However, Prats' system is used to correct and maintain the positioning of the print head on the track in the X direction, i.e., to move the print head back to its original and desired path along the track (in the X direction) in the event that the print head deviates in a Y or Z direction. This is clear from the disclosure of Prats at column 1, lines 38-42, "What was desired, and is provided by this invention, is a control system in which the position of the print head can be both measured and adjusted in any of the x, y, or z translation or rotation directions. This allows very precise printing using a moving print head." Prats makes it additionally apparent at column 3, lines 1-3 that the position control system is designed to *avoid* movement of the print head in the Y or Z direction, "In this way, the print head position control system will detect and correct errors in the movement of the print head as it traverses the track 26 and page 28." Thus, the Prats system is not configured to position the print head in a desired X, Y, or Z direction, but rather is used to correct error offset from the X direction.

In contrast, the positioning system of the present application is capable of positioning the dispenser relative to a localized area on a support. Applicants disclose from page 26, line 42-page 27, line 4 in the application how the positioning system is capable of positioning the dispenser relative to a localized area:

> Starting at a single reference point, the dispenser is translated from one reaction region to other regions of the substrate by a correct distance in the correct direction (this is the "dead reckoning" navigational technique.). At each stop, the dispenser deposits correctly metered amounts of monomer. Analogous systems widely used in the microelectronic device fabrication and testing arts can move at rates of up to 3-10 stops per second. The translational (X-Y) accuracy of such systems is well within 1 μm.

Applicants further disclose at page 27, lines 13-17 how the present positioning system is capable of not only X-Y translational movement, but also, Z directional movement:

> To deposit a drop of monomer solution on the substrate accurately, the dispenser nozzle must be placed a correct distance above the surface. In one embodiment, the dispenser tip preferably will be located about 5-50 μm above the substrate surface when a five nanoliter drop is released.

Accordingly, the present positioning system is capable of moving a dispenser traveling in an X direction to a Y or Z position, whereas the Prats control system moves a print head traveling in an undesired Y or Z position to an X position. Thus, Prats fails to cure the deficiencies of Hayes.

Thus, claims 48-85, 87-110, and 112-123 are patentable because none of the presently cited references, either alone or in combination, teach or suggest the desirability of an automated method of forming an array (or an array of polymers) by dispensing a first monomer in a droplet of less than 5 nl. Accordingly, removal of the present rejection is respectfully requested at this time.

IV. Claims 76, 96, and 111 Are Patentable over Pirrung in View of Sanz and Meltzer

Claims 76, 96, and 111 stand rejected under 35 U.S.C. § 103(a) over Pirrung in view of Sanz and Meltzer. Applicants respectfully traverse this rejection in view of the following remarks.

The Examiner has attempted to place the manually-operated hand-held micropipette of Sanz into the microliter automated pipetting system of Meltzer. One of skill in the art, according to the Examiner, would have done so in order to dispense small volumes into arrays. Applicants respectfully traverse the Examiner's rejection.

Motivation is lacking to make the proposed combination because neither reference suggests the desirability of the modification stated by the Examiner. Further, neither reference makes clear that the proposed modification would be successfully technically feasible and also the proposed modification would impermissibly alter the operability of the devices of Sanz and Meltzer.

It is clear that Sanz teaches a manually operated pipette:

> This intake and delivery system are controlled by rotational movement of the ring 4, in one direction for intake and in the opposite direction for delivery, the quantity of liquid which can be aspirated into or discharged from the tube being set before-hand in particularly accurate manner by suitably positioning the rings 3 and 5 relative to associated fixed references points 8a and 8b (FIG. 15). Column 2, lines 8-14.

Sanz does not disclose the desirability of its device in making arrays. Further, Sanz provides no motivation or direction as to how its highly complex hand-held, presumably heavy, manually operated pipette dispenser is to be automated for any purpose, let alone for the manufacture of arrays. In fact, the complex nature of its manual operation suggests against automation. Further, Sanz provides no direction for including its pipette dispenser into an automated positioning system for dispensing small volumes into arrays even if Sanz could be somehow modified to operate automatically. Sanz, therefore, provides no motivation to use its hand-held manually-operated device in an automated array-making method.

Meltzer makes clear at column 2, lines 64-68, for example, that its positioning system is not only automated but also configured to address tight spacing:

> It is, therefore a principal object of the invention to provide an automated pipetting system having a plurality of independently driven and dispensing probes which fit the tight spacing for multiwell plates and test tube arrays.

In addition, Meltzer admits limitations of its fluid handling system, especially with respect to the quantities of fluid that can be dispensed automatically, at column 9, lines 15-22:

> Pipette tips for the probes may be selected from a range of sizes, such as from 10 to 5000 microliters. The use of **syringe pumps allow fluid quantities as small as 10 µl to be dispensed** with one percent accuracy and quantities of **one microliter** with two percent accuracy when the tip ends are touched on or dipped just below the surface of the fluid in the test tubes to break the liquid surface tension. (Emphasis added).

The state of the art as represented by Meltzer was such that one of skill did not contemplate automated array making devices that could dispense fluid volumes no greater than 5 nl. In addition, Meltzer teaches dispensing by means of touching the pipette tip to the surface of fluid in a test tube *and not by droplets as claimed.* According to Meltzer, its own device could not operate to dispense fluid volumes on the order of 5 nl. Meltzer certainly does not contemplate dispensing volumes on the order of 5 nl or that dispensing such volumes into container arrays would even be desirable. Apparently, the Meltzer fluid handling system becomes less capable of accurately dispensing fluids as the quantity of the fluid dispensed is decreased to just 1 µl. In fact, they state that they are 1% accurate, which at the 10 µl level means +/- 100 nl. Accordingly, Meltzer provides no motivation to modify its dispensing device to create an automated array making device having a dispenser adjusted to dispense droplets no greater than 5 nl. Meltzer certainly provides no motivation to include a manually-operated dispenser as described in Sanz into its device.

In addition, if the Sanz pipette was used in the Meltzer automated system, then the Meltzer automated system would be inoperable for its stated principal intended purpose taught at column 2, lines 64-68:

> It is, therefore, a principal object of the invention to provide an automated pipetting system having a plurality of independently driven and dispensing **probes which fit the tight spacing for multiwell plates and test tube arrays.** (Emphasis added).

Meltzer goes on to explain how its automated system is specially engineered to provide for the tight spacing of the probes and the consequential engineering constraints of the automated system:

> Referring now to FIG. 2a, mounting plate 55a and upper support plate 55b, along with support posts 53a and 53b (FIG. 2c) form the frame for supporting the driving mechanisms for the probes in the form of linear racks 27-1, 27-2, 27-3 and 27-4, shown for one row or probes (FIG. 2a) of preferably eight linear racks 27-1 to 27-8 for eight probes. Stepper motors Z1, Z2, Z3 and Z4 drive the linear racks in the Z-axis direction by means of pinion gears 28-1, 28-2, 28-3 and 28-4 fixed to the output shafts of the respective drive motors 21-24. The motors are arranged in a stacked configuration, one above another, on each side of the row of racks, so as to allow the racks and, therefore, the **probes, to be spaced close together with a spacing corresponding to the standard configuration for test tubes or microwell arrays, typically 0.75 inch on center.** (Emphasis added). Column 8, lines 8-24.

It is thus apparent that the structurally complex Sanz pipettes cannot be easily inserted into the Meltzer automated system if at all, and even if they were, the Meltzer automated system would likely no longer be capable of meeting its prime objective, namely, to fit the tight spacing of multiwell plates and test tube arrays. The Examiner is not allowed to modify the teachings of a reference if the modification renders the reference inoperable for its intended purpose or otherwise changes the principle of operation of the reference. The combination proposed by the Examiner would change the principle of operation of Sanz from a hand-held manually-operated device to an automated device. Similarly, the Meltzer automated pipetting system would be forced to use the manually-operated pipettes of Sanz, which is contrary to the principal of operation of Meltzer. Moreover, neither Sanz nor Meltzer, either alone or in combination, teaches or suggests a positioning system capable of positioning the dispenser relative to a

localized area on the support with the support having one or more localized areas, as defined by independent claims 48 and 116.

In preferred embodiments of the present disclosure, the localized areas have an area on the order of micrometers. In contrast, the Meltzer automated system is configured to dispense into multiwell plates and test tube arrays, which are known by those skilled in the art as being significantly larger than the localized areas taught by Applicants. For example, Meltzer discloses at column 8, lines 19-24 that the standard configuration for test tubes or microwell arrays is typically 0.75 *inch* on center. See column 8, lines 19-24 (quoted above). Further, Meltzer is clearly designed to dispense into containers that will physically contain the deposited fluids, presumably because of the relatively large volumes dispensed. Array production according to the present invention using relatively small volumes dispensed does not require physical containment. Sanz does not cure the deficiencies of Meltzer, as Sanz fails to even teach or suggest any substrate, let alone localized areas, as understood from the present application. Thus, neither reference, either alone or in combination, teaches or suggests localized areas on a support as defined by the pending claims. Accordingly, in view of the foregoing remarks, Applicants respectfully request removal of the present rejection at this time.

V. The Examiner's Request for an Information Disclosure Statement

The Examiner asserts that the Information Disclosure Statement filed March 12, 2002 is missing from the application file and is requesting a copy of the IDS filed March 12, 2002 for completeness of record. As of the date of the present Office Action, Applicants have not filed an IDS in the instant case. In response, Applicants are submitting herewith an Information

Disclosure Statement for filing in the present case. The Examiner is urged to contact the undersigned if further assistance regarding this matter is desired.

VI. Conclusion

Having addressed all outstanding issues, Applicants respectfully request reconsideration and allowance of all claims at this time. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

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